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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/527,352	03/17/2000	Edward L. LeCluyse	421/17/2	3016

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EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/527,352

Applicant(s)

LECLUYSE ET AL.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 5/28/2003 or 9/04/2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 67-200 is/are pending in the application.
- 4a) Of the above claim(s) 67-104 and 119-200 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 105-118 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

The applicants' supplemental filing on 5/28/2003 has crossed in the mail with the office action mailed on 8/08/2003 as evidenced by papers submitted on 9/04/2003. The office action mailed on 8/08/2003 has been issued in response to the applicants' election filed on 5/27/2003. The applicants' supplemental filing on 5/28/2003 contains additional documents (exhibits A-C), declaration and arguments that have been fully considered. New office action is as following.

Status of claims

Claims 105-118 are under examination in the instant office action.

Claims 69-104 and 119-200 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Election was made without traverse in Paper No. 20 filed 5/27/2003.

Claims 12 and 24 were canceled by applicants in the Paper No. 7 filed 9/17/2001. Claims 1-11, 13-23 and 39-66 were canceled by applicants in the Paper No. 13 filed 5/31/2002. Claims 25-38 were canceled by applicants in the Paper No. 18 filed 10/31/2002.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 105-118 are rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al. [11/16/1998; IDS reference CC] or by Dr. Liu's dissertation [June 29, 1998; Exhibit "B" filed 5/28/2003].

Claims are directed to a method of screening a xenobiotic compound for susceptibility to biliary excretion wherein the method comprises steps of establishing two cultures of hepatocytes with intact and disrupted bile canaliculi, exposing both cultures to xenobiotic for a time sufficient to allow uptake of xenobiotic, washing and lysing both cultures, measuring amounts of xenobiotic in lysates of both cultures and calculating/evaluating biliary clearance based on amounts of xenobiotic in lysates of both cultures. Some claims are further drawn to the use of rat hepatocytes, to the use of long-term cultures, to the use of "sandwich" cultures of hepatocytes embedded into matrix medium comprising collagen, to the use of multi-well plate and to the screening a plurality of xenobiotics in the method of screening a xenobiotic compound for susceptibility to biliary excretion.

Liu et al. [IDS-CC, 11/16/1998] disclose a method of screening various xenobiotic compounds including salicylate, inulin, taurocholate, enkephalin, etc. for susceptibility to biliary excretion wherein the method comprises steps of establishing two cultures of rat hepatocytes with intact bile canaliculi (standard buffer) and disrupted bile canaliculi (calcium free buffer), exposing both cultures to xenobiotics for a time sufficient to allow uptake of xenobiotics and measuring amounts of xenobiotics taken by both cultures and further calculating/evaluating biliary clearance based on amounts of xenobiotics taken by both cultures. Although the abstract disclosure is limited and it does not clearly describe step of washing and lysing both cultures, it is reasonably expected that these steps have been performed in order to measure amounts of

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xenobiotics taken by hepatocyte cultures. The hepatocyte cultures of the cited reference are the "sandwich" cultures and they are embedded into matrix with collagen. The hepatocyte cultures are at least 96 hours old and, thus, they are "long-term" cultures according to applicants definitions (page 17, line 13). Thus, the cited reference discloses all claimed steps and structural elements and, therefore anticipates the claimed invention.

Dr. Liu's dissertation [Exhibit B; June 29, 1998] discloses substantially the same method as the reference by Liu et al. [IDS-CC, 11/16/1998] as admitted by applicants (see response page 2, par. 1 and see Declaration, page, it. 6). Thus, the cited document is considered to anticipate the claimed invention.

Claim Rejections - 35 USC § 102/103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 105-118 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over by Liu et al. [IDS-EE, 1997].

Claims are directed to a method of screening a xenobiotic compound for susceptibility to biliary excretion wherein the method comprises steps of establishing two cultures of hepatocytes with intact and disrupted bile canaliculi, exposing both cultures to xenobiotic for a time sufficient to allow uptake of xenobiotic, washing and lysing both cultures, measuring amounts of xenobiotic in lysates of both cultures and calculating/evaluating biliary clearance based on amounts of xenobiotic in lysates of both cultures. Some claims are further drawn to the use of rat

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hepatocytes, to the use of long-term cultures, to the use of "sandwich" cultures of hepatocytes embedded into matrix medium comprising collagen, to the use of multi-well plate and to the screening a plurality of xenobiotics in the method of screening a xenobiotic compound for susceptibility to biliary excretion.

Liu et al. [IDS-EE, 1997] disclose a method of screening various xenobiotic compounds belonging to different classes including alanine, morphine, salicylate, inulin, mannitol, taurocholate, enkephalin, etc. for susceptibility to biliary excretion wherein the method comprises steps of establishing two cultures of rat hepatocytes having intact bile canaliculi (standard solution HBSS with calcium) and having disrupted bile canaliculi (calcium free solution HBSS), exposing both cultures to xenobiotics for a time sufficient to allow uptake of xenobiotics and measuring amounts of xenobiotics taken by both cultures and further evaluating/calculating xenobiotic amounts retained/excreted into bile canaliculi based on amounts of xenobiotics taken by both cultures with and without bile canaliculi. Although the abstract does not clearly describe step of washing and lysing both cultures, it is reasonably expected that these steps have been performed in order to measure amounts of xenobiotics taken by both hepatocyte cultures. The hepatocyte cultures of the cited reference are the "sandwich" cultures and they are embedded into matrix with collagen. The hepatocyte cultures are at least 5 day old and, thus, they are "long-term" cultures according to applicants definitions (page 17, line 13).

However, the particular index which is calculated in the end of the method of the cited reference is a "biliary excretion" index but not a "biliary clearance" index as encompassed by the claimed invention. But, according to the applicants' definitions (page 19, last paragraph or page

32, equation 4), evaluation of "biliary clearance" requires measurements of the same amounts of test compounds which are retained in the intact canalicular network as the amounts measured in the method of the cited reference. Thus, it appears that the method of the cited reference results in the possession of the same measurable values and of the same evaluation as required by the presently claimed method. In addition, the applicants' definition of a "biliary clearance" index also requires knowledge of a time period of exposure of the hepatocyte cultures to the test compound and knowledge of concentration of xenobiotics in order to evaluate/calculate "biliary clearance". However, the cited reference teaches a time period of exposure, for example: 10 minutes and, further, it is reasonably believed that test xenobiotic concentrations have been available before the testing or screening method.

Thus, the method of the cited reference appears to be identical to the presently claimed method and is considered to anticipate the claimed microorganism since it comprises the same structural elements and the same active steps as the claimed method.

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In the alternative, even if the claimed method is not identical to the referenced method with regard to particular calculation of a "biliary clearance" index, the differences between that which is disclosed and that which is claimed are so slight that all measurable values obtained by the method of the cited reference allow for calculation/evaluation of the same "biliary clearance" value or index as intended for the present invention. Thus, the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103. Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claim Rejections - 35 U.S.C. § 103

Claims 105-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. [IDS-CC, 11/18/1998] or Dr. Liu's dissertation [Exhibit B; June 29, 1998] and Liu et al [IDS-EE, 1997] taken with US 5,602,026 [A].

Claims are directed to a method of screening a xenobiotic compound for susceptibility to biliary excretion wherein the method comprises steps of establishing two culture of hepatocytes with intact and disrupted bile canaliculi, exposing both cultures to xenobiotic for a time sufficient to allow uptake of xenobiotic, washing and lysing both cultures, measuring amounts of xenobiotic in lysates of both cultures and calculating/evaluating biliary clearance based on amounts of xenobiotic in lysates of both cultures. Some claims are further drawn to the use of hepatocytes derived from various animals, to the use of long-term cultures, to the use of "sandwich" cultures of hepatocytes embedded into matrix medium comprising collagen, to the use of multi-well plate and to the screening a plurality of xenobiotics in the method of screening a xenobiotic compound for susceptibility to biliary excretion.

The cited references Liu et al.[IDS-CC, 11/18/1998], Dr. Liu's dissertation [Exhibit B; June 29, 1998] and Liu et al. [IDS-EE, 1997] are relied upon as explained above. They appear to lack disclosure with regard to the use of various hepatocytes including animal and human hepatocytes.

US 5,602,026 [A] is relied upon for the disclosure of culturing or maintaining rat and human hepatocytes in sandwich configuration with bile canalicular network (col. 7, lines 65-67). The cited patent teaches that the sandwich culture of hepatocytes has metabolic function of the liver *in vivo* (col.8, line 23) and that the sandwich culture is suitable for studying hepatocyte metabolism and recovering product of hepatocyte metabolism (col. 8, line 33). In addition, the cited patent suggests various extracellular matrix components (col. 8, lines 38-41).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use various hepatocytes including animal and human hepatocytes in the methods of screening test xenobiotic compounds for susceptibility to biliary excretion of the references Liu et al. [IDS-CC, 11/18/1998], Dr. Liu's dissertation [Exhibit B; June 29, 1998] and/or Liu et al [IDS-EE, 1997] with a reasonable expectation of success in investigating susceptibility of test compounds in various animal systems because the sandwich cultures of various hepatocytes including animal and human hepatocytes have been known and suggested for various screening assays as adequately demonstrated by US 5,602,026 [A]. One of skill in the art would have been motivated to use human hepatocyte culture *in vitro* systems for the expected benefit in predicting biliary excretion of test compounds in the *in vivo* systems and to investigate interaction of test compounds relevant to biliary excretion as suggested by Liu et al [IDS-EE, 1997] (see last three lines).

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Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicants' declaration and arguments filed on 5/28/2003 have been fully considered but they are not persuasive.

Declaration pursuant to 37 CFR 1.131-1.132 has been fully considered particularly as related to overcome prior art rejection based on the reference by Liu et al. [IDS-CC, 11/16/1998]. Applicants have provided Dr. Liu's dissertation {Exhibit B} that was defended on June 29, 1998. However, the issue of co-authorship remains uncertain. The instant application, the reference by Liu et al. [IDS-CC, 11/16/1998] and the dissertation have different inventive entities and, thus, the references by Liu et al. [IDS-CC, 11/16/1998] and the Dr. Liu's dissertation are the prior art references by "others" within the meaning of 35 USC 102. Therefore, the dissertation by Dr. Liu has been also applied in the claim rejection in the instant office action.

With regard to the reference by Liu et al. [IDS-EE, 1997] applicants appear to argue that the measurements for determination of the biliary excretion index are not and/or would not be the same as the measurements for determination of the biliary clearance value (see Declaration page 2, it. 9). Yet, the differences in measuring these parameters or activity values are unclear as claimed and as argued. Further, the applicants' arguments (see Declaration pages 2-3, it. 10) based on the distinct nature of calculations do not provide persuasive grounds because

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calculations are mental evaluations of the same actual measurements or parameters obtained either for the biliary excretion index as disclosed by the cited reference Liu et al. [IDS-EE, 1997] or for the biliary clearance value as presently claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351 till January 15, 2004 or (571) 271-0914 after January 15, 2004. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743 till January 15, 2004 or on (571) 272-0926 after January 15, 2004.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova



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VERA AFREMOVA

December 24, 2003.

PATENT EXAMINER